REMARKS

STATUS OF THE CLAIMS

Claims 18-28 are pending. Claims 18-21 stand rejected under 35 U.S.C. § 102(e).

SPECIFICATION

The specification was objected to as allegedly failing to provide proper antecedent basis for the amendments to the claim 18 and claims 24-28. (Final Office Action, page 2). In particular, it is maintained that the terminology in these claims is not found in the present specification. *Id.*

Applicants strongly disagree that the claims lack antecendent basis or that the terminology used is not clearly found in the specification as filed. Although not specified in the Final Office Action, Applicants assume that the Examiner is objecting to the terms "selectively cleavable link" and/or "selectively cleavable site."

As clearly set forth in 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(o), an issue of support arises only in instances where the use of the terminology in the claims departs from usage in the as-filed specification. The requirement that the specification and claims use terms consistently is to insure certainty in construing the claims in the light of the specification. *See, also,* M.P.E.P. § 608.01(o) citing *Ex parte Kotler*, 1901 C.D. 62, 95 O.G. 2684 (Comm'r Pat. 1901).

In the pending case, there is no uncertainty in claim construction because the as-filed specification clearly and unambiguously uses the terms "selectively cleavage link" and "selectively cleavable site" as used in the claims to refer to an amino acid sequence of a fusion protein that is placed between two other proteins to allow for cleavage between the two proteins:

> The two polypeptides contained in the expression product may be joined by a **selectively cleavable link**, so that the two polypeptides may be separated to provide for high yield of each of the polypeptides. (page 3, lines 3-6, emphasis added)

> Novel methods and compositions are provided for enhancing the production of heterologous products in eukaryotic organisms, particularly yeast or prokaryotic organisms, such as E. coli, by employing sequences encoding for a polypeptide, which is a combination of two polypeptide regions joined by a **selectively cleavable site**. (page 3, lines 14-19, emphasis added)

> Where the two genes are obtained in-whole or in-part from naturally occurring sources, it will be necessary to ligate the two genes in proper reading frame. If cleavage of the fused protein is required, where their juncture does not define a **selectable cleavage site**, genes will be separated by a **selectively cleavable site**. The **selectively cleavable site** will depend to some degree on the nature of the genes. That is, the means for cleaving may vary depending upon the amino acid sequence of one or both genes. (page 5, lines 17-27, emphasis added)

> The cells may be grown until there is no further increase in product formation or the ratio of nutrients consumed to product formation falls below a predetermined value, at which time the cells may be harvested, lysed and the fused protein obtained and purified in accordance with conventional techniques. These techniques include chromatography, e.g., HPLC; electrophoresis; extraction; density gradient centrifugation, or the like. Once the fused protein is obtained, it will then be **selectively cleaved** in accordance with the nature of the **selectively cleavable linkage**. This has been described previously in relation to the description of the various linkages. (page 14, lines 10-22, emphasis added).

Furthermore, the specification clearly supports the particular cleavable links set forth in the claims 24-48:

> One of the methods for selectable cleavage is cyanogen bromide which is described in U.S. Pat. No. 4,366,246. This technique requires the absence of an available methionine other than at the site of cleavage or the ability to selectively distinguish between the methionine to be cleaved and a methionine within the polypeptide sequence. Alternatively, a protease may be employed which recognizes and cleaves at a site identified by a particular type of amino acid. Common proteases include trypsin, chymotrypsin, pepsin, bromelain, papain, or the like. Trypsin is specific for basic amino acids and cleaves on the carboxylic side of the peptide bond for either lysine or arginine. Further, peptidases can be employed which are specific for particular sequences of amino acids, such as those peptidases which are involved in the selective cleavage of secretory leader signals from a polypeptide. These enzymes are specific for such sequences which are found with α-factor and killer toxin in yeast, such as KEX 2 endopeptidase with specificity for pairs of basic residues (Julius et al., Cell (1984) 37:1075-1089). Also, enzymes exist which cleave at specific sequences of amino acids. Bovine enterokinase (Light et al., Anal. Biochem. (1980) 106:199-206) cleaves to the carboxylic side of lysine or arginine that is preceded by acid residues of aspartic acid, glutamic acid, or carboxymethyl cysteine. Particularly useful is the sequence $(Asp)_4$ Lys found naturally as part of the activation peptide of trypsinogen in many species. Other enzymes which recognize and cleave specific sequences include: Collagenase (Germino and Batia, Proc. Natl. Acad. Sci. (1984) 81:4692-4696); factor X (Nagai & Thygersen, Nature (1984) 309:810-812); and polyubiquitin processing enzyme (Ozakaynak et al., Nature (1984) 312:663-666). (page 7, line 21 to page 8, line 21).

Thus, the amendments to the claims in no way depart from the usage of the terminology found in the as-filed specification and the claims can be readily construed in light of the specification. Therefore, Applicants respectfully request that this objection be withdrawn.

OATH/DECLARATION

The Examiner asserts that a supplemental oath or declaration is required. For the reasons noted above, Applicants submit that the pending claims are fully supported by the specification as filed and, accordingly, a new oath is not required.

DOUBLE PATENTING

Applicants request that the double patenting rejection be held in abeyance until indication of allowable subject matter.

35 U.S.C. § 102(e)

Claims 18-21 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,252,476 (hereinafter "Hallewall"). (Office Action, page 3). In support of this rejection, the Examiner states:

> Hallewall et al. discloses production of human superoxide dismutase fused to additional amino acids (for example a heterologous secretory signal sequence) in a variety of host cells including yeast, *E. coli* and *B. subtilis*. see abstract; claims; columns 2-3; column 6, line 51 through column 7, line 2. Such a heterologous secretory signal sequence would meet the limitation of a selectively cleavable link wherein said link provides for a selectively cleavable site.

Applicants traverse the rejection and supporting remarks.

In order to be an anticipatory reference, the reference cited by the Office must disclose each and every element of the claims, including each and every functional or biological limitation. *See, e.g., Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986); M.P.E.P § 2173.05(g) Functional Limitations, Eighth Edition. Moreover, the single source must disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989). Simply put, the law requires identity as between the prior art disclosure and the invention. *See, e.g., Kalman v. Kimberly-Clark Corp.* 218 USPQ 781 (Fed. Cir. 1983), *cert. denied*, 484 US 1007 (1988). Further, to support an anticipation rejection based on inherency, the Office must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the reference. *See, e.g., Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990). Inherency cannot be established by probabilities or possibilities. *See, e.g., Continental Ca Co. USA, Inc. v. Monsanto Co.* 20 USPQ2d 1746, 1749 (Fed. Cir. 1987). Thus, the references must teach all elements of the claims, explicitly or inherently, including functional limitations such as biological function.

Applicants submit that the Office has not met its burden of establishing a *prima facie* case of anticipation because Hallewall does not inherently disclose the required use of selectively cleavable link to cleave two proteins of a fusion protein. As noted above, it is well established that, under the doctrine of inherency, a reference can anticipate a claim if and only if the missing element is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Rosco Inc. v. Mirror Lite Co.*, 64 USPQ2d 1676 (Fed. Cir. 2002) citing *Cont'l Can Co. v. Monsanto Co.*, 20 USPQ2d 1746 (Fed. Cir. 1991). In other words, inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 63 USPQ2d 1597 (Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)).

In the pending application, the molecules of claims 18-21 must include two fusion proteins separated by a selectively cleavable linkage sequence. Thus, the question is not whether Hallewall discloses SOD sequences that may include additional processing sequences, but whether one skilled in the art would read these references as necessarily disclosing use of a selectively cleavable link to separate two proteins of a fusion protein. In point of fact, there is absolutely no evidence in the record to support a finding that one skilled in the art would so read Hallewall. Indeed, Hallewall is concerned with expression of SOD, not with a fusion of SOD and another protein, which proteins must be separated. Thus, because the concept of a separating two proteins using a selectively cleavable link is absent from Hallewall and cannot inevitably flow from this disclosure, Hallewall does not in any way inherently disclose the molecules of claims 18-21.

The anticipation rejections based on alleged inherency are also improper because no evidence has been offered by the Office supporting the assertion that secretory sequences will function as selectively cleavable links. As the Board of Patent Appeals and Interferences and Federal Circuit have repeatedly established, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic" of the reference. *Ex parte Skinner,* 2 USPQ2d 1788 (BPAI 1986), emphasis added. The Office has provided no such evidence or reasoning, but, instead, has merely asserted that any reference related to SOD inherently discloses the particularly claimed invention of claims 18-21. In the absence of any evidence supporting inherency and the abundance of evidence against inherency, Applicants submit that the rejection is improper and should be withdrawn. In the event that the Examiner continues to maintain these unsupported rejections, Applicants request, pursuant to 37 C.F.R. § 1.104(d)(2), that the Examiner support this rejection with an affidavit.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

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